method, and

[said] the diffraction data measured in step (g) is analyzed using a multiwavelength anomalous diffraction phasing method.--

--11.(Amended) A process according to claim 10, wherein selenomethionine is incorporated in the [synthesized] plurality of target proteins synthesized in step (c), and [said] the multiwavelength anomalous diffraction phasing method is used to analyze [said] diffraction data [of] measured for selenomethionyl proteins.--

--12.(Amended) A process according to claim 7, further comprising the step of

using [said] the homology model developed in step (i) in at least one of target selection, drug design, and design of more appropriate constructs for experimental analysis.--

REMARKS

Claims 1 through 12 are pending and presently under examination in the subject application. Applicants have hereinabove amended claims 1 through 12.

Applicants maintain that no new matter is presented by this amendment. Accordingly, applicants respectfully request that this Amendment be entered.

October 19, 1999 Information Disclosure Statement

Applicants filed an Information Disclosure Statement on October 19, 1999. Attached hereto as **Exhibit A** is a copy of the returned postcard bearing the stamp of the Patent and Trademark Office which indicates receipt of the October 19, 1999 Information Disclosure Statement by the Patent and Trademark Office.

At the time that the Information Disclosure Statement was filed on October 19, 1999, applicants and the undersigned were not aware of the issuance of the October 6, 1999 Office Action.

Applicants believe that neither a final action nor a notice of allowance has been issued by the Patent and Trademark Office to date. Applicants hereby request entry and consideration of the October 19, 1999 Information Disclosure Statement, if the October 19, 1999 Information Disclosure Statement has not already been entered and considered by the Patent and Trademark Office, pursuant to 37 C.F.R. §1.97(c)(2). The Patent and Trademark Office fee under 37 C.F.R. §1.17(p) for submission of an Information Disclosure Statement after issuance of a first Office Action is TWO HUNDRED FORTY DOLLARS ($240). Authorization is hereby given to charge, to the extent not already charged, the amount of the fee under 37 C.F.R. §1.17(p) to Deposit Account No. 03-3125.

Objection to the Oath/Declaration

In Section 1 of the October 6, 1999 Office Action, the Examiner stated that the oath or declaration is defective because the original signatures were missing. The Examiner suggested resubmitting a new oath or declaration in compliance with 37 C.F.R. §1.67(a) identifying the application by application number and filing date.

In response, applicants will submit a new oath or declaration in compliance with 37 C.F.R. §1.67(a) identifying the application by application number and filing date in due course.

Objection To The Abstract

In Section 2 of the October 6, 1999 Office Action, the Examiner objected to the abstract of the disclosure. The Examiner stated that the length of the abstract is in excess of 250 words.

In response, without conceding the correctness of the Examiner's position, but solely to advance prosecution of the subject application, applicants have amended the abstract of the disclosure. Accordingly, applicants respectfully request that the Examiner withdraw the objection to the abstract of the disclosure.

Rejection Under 35 U.S.C. §112, Second Paragraph

In Section 4 of the October 6, 1999 Office Action, the Examiner rejected claims 1-12 under 35 U.S.C. § 112, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner stated that claims 1 and 7 are drawn to a system and method, respectively, with the limitation of pan-genomic determination, wherein "all known structural information" is utilized. The Examiner also stated that applicants' use of the term "all known structural information" is unclear since it is impossible to anticipate what structural parameters would be relevant in any one case of practicing the claimed invention. The Examiner further stated that all dependent claims were rejected on the aforementioned grounds.

In response, without conceding the correctness of the Examiner's position but solely to advance the prosecution of the subject application, applicants have hereinabove amended claims 1 and 7 to delete "all" from the term "all known structural information". Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-12 under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. §112, Second Paragraph

In Section 5 of the October 6, 1999 Office Action, the Examiner rejected claims 1-12 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner stated that claims 1 and 7 are drawn to a system and method, respectively, with the limitation of pan-genomic determination, wherein an ensemble of all known structures is utilized to "further advance an effectiveness of said bioinformatics." The Examiner also stated that all dependent

claims were rejected on the aforementioned grounds.

In response, without conceding the correctness of the Examiner's position but solely to advance the prosecution of the subject application, applicants have hereinabove amended claims 1 and 7 to delete "an ensemble of all known structures is used to further advance an effectiveness of said bioinformatics tools". Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-12 under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 103(a)

In Section 7 of the October 6, 1999 Office Action, the Examiner rejected claims 1-12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,878,373 issued to Cohen et al. (hereinafter "Cohen '373").

The Examiner stated that Cohen '373 discloses a system and a method for predicting the protein fold of a target amino acid sequence, where the experimental 3D structure is undetermined, with a catalogued protein structure. The Examiner stated that the target sequence is represented by both positional strings and tertiary attributes. The Examiner stated that the target is compared against the 3D structures of the "known" structures available in a database by using a dynamic programming procedure to calculate a best fit score indicating the outcome of alignment. The Examiner stated that by implementing residue variability parameters, the purportedly inventive method in Cohen '373 allegedly has extended capabilities over conventional alignment strategies that identify structural similarities between proteins. The Examiner stated that the structural properties of the proteins could be compared between proteins classified in the same family, although family classification is subjective, or between proteins that typically lack a common grouping. The Examiner further alleged that the invention meets the limitations of applicants' system/method of pan-genomic determination of three-dimensional structures comprising a

database that systematically organizes all known structural information into a genomic database, and uses the "functional information" to cluster a plurality of known gene products. The Examiner alleged that it is inherent in the cited art that the most closely related matches of multiple known structures to the unknown structure, would often be of the same family themselves. The Examiner stated that, thus, any number of "functional parameters" allegedly could be used in classification or a particular grouping that is in actuality user-defined.

The Examiner acknowledged that Cohen '373 does not disclose a system/method for (1) protein synthesis; (2) protein screening; (3) protein processing; (4) crystallization; and (5) x-ray crystallography.

The Examiner alleged that systems for the means of: (1) protein synthesis; (2) protein screening; (3) protein processing; (4) crystallization; and (5) x-ray crystallography, are all well-established in the art as cited by applicants in the specification of the current application.

The Examiner also alleged that from the teaching of the references on methods and systems for predicting/comparing the 3D structure of a query sequence, or as a means of classification, from the association of the query primary sequences with sequences of known 3D structure, it is obvious that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The Examiner further alleged that, one of ordinary skill in the art would have been motivated to combine the teachings of Cohen `373 with any well-established systems/methods to produce a method/system which applies sequence position and tertiary characteristics to both the known and unknown 3D sequences as a means for determining the unknown 3D sequence with alignment algorithms, and for family classifications, with the improvement of the well-established system/method. The Examiner alleged that the systems/methods for the means of (1) protein synthesis; (2)

protein screening; (3) protein processing; (4) crystallization; and (5) x-ray crystallography are all well-established in the art as cited by applicants in the specification of the current application. The Examiner then stated that the linking or association of multiple well-known inventions into a single invention does not necessarily merit a patent. The Examiner stated that, however, unexpected results from the combination of well-known inventions can lend patentable weight to an application. The Examiner alleged that these claims are an obvious variant of Cohen '373. The Examiner stated that applicants have not shown any evidence in the data presented in the specification which represents a non-obvious or unexpected practical advantage of the claimed invention over the prior art. The Examiner suggested that if applicants believe that there are unexpected results due to the precise combination of the systems/methods as claimed, applicants are invited to point out specifically to the specification and cite the unexpected improvement over the art. The Examiner alleged that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully traverse the rejection of claims 1 through 12 under 35 U.S.C. §103(a).

The subject invention provides a process/system for determining experimentally, at a high throughput, the unknown three-dimensional structure of target proteins. Appropriately representative members are selected from families of proteins as the target proteins. Known information regarding the target proteins are used to synthesize the target proteins. The synthesized constructs are then screened to determine those that are effective as proteins. The effective proteins are prepared, purified and characterized. Each purified target protein is set to crystallize in parallel against crystallization screens. Crystals that grow are tested for suitable diffraction characteristics. The suitable crystals of the target protein are frozen, and high-throughput crystallography is performed on the

frozen crystals. Diffraction data are measured and analyzed, an atomic model of the target protein is built and refined against the diffraction data.

Cohen '373 appears to describe a system and method for, as the Examiner noted, predicting the protein fold of a target amino acid residue sequence of unknown protein structure. Cohen '373 teaches mapping the target sequence into a sequence of one of a predetermined number of residue variability types, which are based on solubility and/or positional variability. The sequence is then compared with one or more environment strings, each of which characterizes a corresponding known protein structure with respect to the degree of surface exposure of each amino acid in the protein's structure. The target sequence of residue variability types is aligned to each environment string using a threading procedure. A score is calculated indicating the outcome of the alignment. The protein structure associated with the highest best fit score indicates the most analogous protein structure of the target sequence.

Although Cohen '373 appears to describe a system and method for predicting the protein fold of a target amino acid residue sequence of unknown protein structure, Cohen '373 neither describes nor suggests, however, a system or a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by applicants' claimed invention set forth in amended claims 1 and 7. As applicants pointed out at, for example, page 4, lines 11-16 of the specification, computational structural predictions, as taught for example in Cohen `373, would not have an accuracy comparable to experimental determination of structures at least until a comprehensive structure database is developed.

Cohen '373, as the Examiner acknowledged, fails to describe or suggest many of the elements that are provided by applicants' invention for determining experimentally a plurality of three-

dimensional atomic structures of proteins.

Cohen '373 fails to describe the following elements of applicants' claimed system for determining experimentally a plurality of three-dimensional atomic structures of proteins: (1) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool, in parallel, a plurality of target proteins, which are appropriately representative members of the family, using information stored in the database corresponding to the target proteins, the protein synthesis means having screening means for screening the products of the synthesis to determine ones that are effective as proteins; (2) protein processing means for preparing, purifying and characterizing each target protein which is determined to be effective by the screening means; (3) crystallization means for crystallizing each target protein processed by the protein processing means in parallel against a plurality of crystallization screens to produce a plurality of specimen crystals of the target protein, and testing the plurality of specimen crystals for predetermined diffraction characteristics to determine suitable ones of the plurality of specimen crystals of the target protein; and (4) X-ray crystallography means for performing high-throughput crystallography on the specimen crystals of each target protein determined by the crystallization means to be suitable, the X-ray crystallography means having diffraction measuring means for measuring for diffraction data the suitable specimen crystals of the target protein, analyzing means for analyzing the diffraction data, means for building an atomic model of the target protein according to an analysis of the diffraction data by the analyzing means, and means for refining the model of the target protein against the diffraction data and storing the refined model in the database, as provided by the invention set forth in amended claim 1.

Cohen '373 also fails to teach each of the following steps in applicants' claimed process for determining experimentally a plurality of three-dimensional atomic structures of proteins: (c)

synthesizing for each family determined in step (b), in parallel, a plurality of target proteins, which are appropriately representative members of the family, using information stored in the database corresponding to the plurality of target proteins, and screening products of the synthesis to determine ones that are effective as proteins; (d) preparing, purifying and characterizing each target protein which is determined to be effective in step (c); (e) crystallizing each target protein prepared, purified and characterized in step (d) in parallel against a plurality of crystallization screens to produce a plurality of specimen crystals of the target protein; (f) testing the plurality of specimen crystals of one of the target proteins grown in step (e) for predetermined diffraction characteristics to determine suitable ones of the plurality of specimen crystals of the one target protein; (g) performing high-throughput crystallography, including measuring for diffraction data the specimen crystals of the one target protein determined in step (f) to be suitable, building an atomic model of the one target protein according to an analysis of the diffraction data, refining the model of the one target protein against the diffraction data, and storing the refined model in the database; and (j) performing steps (f) through (i) for each of the other target proteins, as provided by the invention set forth in amended claim 7.

The Examiner apparently is of the opinion that the means/steps for the following which are recited in claims 1 and 7 are well-known in the art and it allegedly would have been obvious to combine the teachings of Cohen `373 with these means/steps as recited in the claims: (1) protein synthesis; (2) protein screening; (3) protein processing; (4) crystallization; and (5) x-ray crystallography. Applicants respectfully disagree.

Applicants submit that there would not have been motivation for combining the system and method, described in Cohen '373, for predicting the protein fold of a target amino acid residue sequence of unknown protein structure, with the elements in a

system and/or the steps in a process for determining experimentally a plurality of three-dimensional atomic structures, without using applicants' invention as a roadmap. Although Cohen '373 states at column 1, lines 40-43 that the three-dimensional structure of proteins has been determined in a number of ways, including using the technique of X-ray crystallography, Cohen '373 also acknowledges at column 2, lines 5-26 that even though there has been a well-recognized need for a means for readily determining a protein's three-dimensional structure from its amino acid sequence, that need has not been adequately met by the then-known techniques of protein structure determination. Thus, it is submitted that one skilled in the art following the teachings of Cohen `373 would not have been motivated to combine, and indeed would have been taught away from combining, the system/method, described in Cohen '373, for predicting the protein fold of a target amino acid residue sequence of unknown protein structure, on the one hand, and elements/steps for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7, on the other hand.

Further, even in its general discussion of X-ray crystallography techniques known in the art, Cohen `373 does not suggest combining the system/method, described in Cohen `373, for predicting the protein fold of a target amino acid residue sequence of unknown protein structure, with elements/steps for determining experimentally three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7. Cohen '373 simply does not suggest or provide motivation for a system/process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7.

Since Cohen '373 fails to suggest or provide motivation for a

system or a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7, it would not have been obvious to combine the system/method described in Cohen '373 with elements/steps, even if the elements/steps individually are known generally to the art, for determining experimentally a plurality of three-dimensional atomic structures, in the manner suggested by the Examiner, without using the claimed invention as a template.

Applicants maintain that claims 1 and 7 are patentable over Cohen '373.

Regarding claims 2 through 6 applicants respectfully point out that claims 2-6 depend on and include all the limitations of claim 1. Thus, claims 2-6 are patentable at least for the reasons set forth above with respect to claim 1.

Regarding claims 8 through 12 applicants respectfully point out that claims 8-12 depend on and include all the limitations of claim 7. Thus, claims 8-12 are patentable at least for the reasons set forth above with respect to claim 7.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-12 under 35 U.S.C. § 103(a).

Rejection Under 35 U.S.C.§103(a)

In Section 8 of the October 6, 1999 Office Action, the Examiner rejected claims 1-12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,436,850 issued to Eisenberg et al. (hereinafter "Eisenberg '850") in view of Kreisberg et al., Protein Science, 4, pp. 2405-2410, 1995 (hereinafter "Kreisberg paper").

The Examiner stated that Eisenberg '850 discloses a computer

assisted method for identifying protein sequences that fold into a known three-dimensional structure through attacking the "inverse protein folding" problem. The Examiner stated that the method described by Eisenberg '850 compares the amino acid sequences of a known three-dimensional structure to the amino acid sequence of unknown three-dimensional structure. The Examiner stated that, specifically, Eisenberg '850 describes at column 3, line 61 through column 4, line 52 provides a method for relating one-dimensional query sequences directly to known 3D structures which utilize information as it pertains to particular structural characteristics. The Examiner stated that the structural characteristics considered by Eisenberg '850 include: (1) the accessibility of residues to solvent; (2) polarity of residues; and (3) the local secondary structure. The Examiner stated that Eisenberg '850 also teaches a "Z-score" which is the number of standard deviations that, for a "best fit" alignment score of the known sequence, is above the mean alignment score for other known sequences of similar length. The Examiner stated that these characteristics are represented by an environmental string of data so that a "best fit" alignment score between known 3D sequences can be compared to the 1D structure of the query sequence. The Examiner stated that, in other words, Eisenberg '850 utilize a method which brings into consideration both sequence position *and* tertiary characteristics of known 3D sequence. The Examiner stated, however, only information pertaining to the primary structure of the sequence corresponding to which the 3D structure is unknown is utilized in the alignment algorithms.

The Examiner acknowledged that Eisenberg '850 does not teach the advantages of using secondary or tertiary characteristics, assigned or derived, for the amino acids or amino acid sequence of the query.

The Examiner also stated that the Kreisberg paper teaches a method that is an improvement upon a method of aligning a primary structure of a protein to a protein of a known 3D structure. The

Examiner stated that the improvement comprises imposing secondary structural aspects upon the query sequence as a means to assist alignment for structure predictions. The Examiner stated that the Kreisberg paper states on page 2406 beginning of second full paragraph as follows:

> "For proteins of unknown architecture, knowing which cysteine pairs are disulfide bonded in primary sequences containing more than two cysteines can facilitate the prediction of tertiary structure."

The Examiner stated that the improvements of this method are described in the Kreisberg paper at page 2407, sixth full paragraph, where the field of the search was reduced considerably through associating conserved cysteines between the query sequence and the known 3D structures. The Examiner stated that, furthermore, the Kreisberg paper at page 2409, first full paragraph suggests that any constraint, such as solvent accessibility and hydrophobic moments, including disulfide bridges, may be useful for assisting the 3D structures in queries.

The Examiner also stated that the Kreisberg paper not only teaches a method for aligning an unknown sequence to a known sequence in a given database, but discloses at page 2407, starting with the second full paragraph a method for drawing structural relationships between protein families. The Examiner stated that the Kreisberg paper describes a method that compares sequences with varying degrees of homology within a protein family, and illustrates how a more comprehensive database with respect to the method of classification is advantageous in determining unknown sequence relationships/structures.

The Examiner alleged that from the combined teachings of Eisenberg '850 and the Kreisberg paper on methods and systems for predicting/comparing the 3D structure of a query sequence, or as a means of classification, from the association of the query primary sequences with sequences of known 3D structure, it is purportedly obvious that one of ordinary skill in the art would

have had a reasonable expectation of success in producing the claimed invention. The Examiner stated that one of ordinary skill in the art would have been motivated to combine the teachings of Eisenberg '850 with the teachings of the Kreisberg paper to produce a method which applies sequence position *and* tertiary characteristics to both the known and unknown 3D sequences as a means for determining the unknown 3D sequence with alignment algorithms, and for family classifications. The Examiner stated that, additionally, systems for the means of: (1) protein synthesis; (2) protein screening; (3) protein processing; (4) crystallization; and (5) x-ray crystallography, are all well-established in the art as cited by applicants in the specification of the current application. The Examiner stated that the linking or association of multiple, well-known inventions into a single invention does not necessarily merit a patent. The Examiner stated that however, unexpected results from the combination of well-known inventions can lend patentable weight to an application. The Examiner stated that, therefore, the claims are an obvious variant of Cohen '373. The Examiner stated that applicants have not shown any evidence in the data presented in the specification which represents a non-obvious or unexpected practical advantage of the claimed invention over the prior art. The Examiner stated that if applicants believe that there are unexpected results due to the precise combination of the systems/methods as claimed, applicants are invited to point specifically to the specification including the page and line numbers, and cite the unexpected improvement over the art. The Examiner alleged that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully traverse the rejection of claims 1 through 12 under 35 U.S.C. §103(a).

Eisenberg '850 appears to describe a method for predicting the unknown structure of a protein, of which the (target) amino acid sequence is known and which may be only distantly related to

other protein structures which are known. The method described in Eisenberg `850 starts with determining the following key features of each residue's environment within one of the known three-dimensional protein structures: (1) the total area of the residue's side-chain that is buried by other protein atoms, inaccessible to solvent; (2) the fraction of the side-chain area that is covered by polar atoms (O, N) or water, and (3) the local secondary structure. Based on these parameters, the three-dimensional protein structure is converted into a one-dimensional environment string, which represents the environment class of each residue in the folded protein structure. A 3D structure profile table is then created containing score values that represent the frequency of finding any of the twenty common amino acids structures at each position of the environment string. These frequencies are determined from a database of known protein structures and aligned sequences. Once the profile table is generated for a protein sequence having a known 3D structure, a comparison may be made between the table and the target amino acid sequence having unknown structure. The profile table may be used to determine the most favorable alignment of the target sequence to the residue positions defined by the environment string, and determine a "best fit" alignment score for the target sequence. The quality of alignment is taken as a measure of the compatibility (i.e. prediction of the similarity of the unknown structure) of the target sequence with the known three-dimensional structure upon which the environment string was based.

Although Eisenberg `850 appears to describe a method for predicting the unknown structure of a protein, of which the (target) amino acid sequence is known, Eisenberg `850 neither describes nor suggests, however, a system or a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7.

The Kreisberg paper appears to describe prediction of three-dimensional protein structures which are unknown, by using paired natural-cysteine-mutation maps that identify the positions of putative disulfide bonds in known primary sequences in the protein family. The Kreisberg paper, like Eisenberg '850, neither describes nor suggests, however, a system or a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7.

Eisenberg '850 and the Kreisberg paper each, as the Examiner appears to acknowledge, fails to describe or suggest many of the elements that are provided by applicants' invention for determining experimentally a plurality of three-dimensional atomic structures of proteins.

Eisenberg '850 and the Kreisberg paper each fails to teach each of the following elements of applicants' claimed system for determining experimentally a plurality of three-dimensional atomic structures of proteins: (1) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool, in parallel, a plurality of target proteins, which are appropriately representative members of the family, using information stored in the database corresponding to the target proteins, the protein synthesis means having screening means for screening the products of the synthesis to determine ones that are effective as proteins; (2) protein processing means for preparing, purifying and characterizing each target protein which is determined to be effective by the screening means; (3) crystallization means for crystallizing each target protein processed by the protein processing means in parallel against a plurality of crystallization screens to produce a plurality of specimen crystals of the target protein, and testing the plurality of specimen crystals for predetermined diffraction characteristics to determine suitable ones of the plurality of specimen crystals of the target protein; and (4) X-ray

crystallography means for performing high-throughput crystallography on the specimen crystals of each target protein determined by the crystallization means to be suitable, the X-ray crystallography means having diffraction measuring means for measuring for diffraction data the suitable specimen crystals of the target protein, analyzing means for analyzing the diffraction data, means for building an atomic model of the target protein according to an analysis of the diffraction data by the analyzing means, and means for refining the model of the target protein against the diffraction data and storing the refined model in the database, as provided by the invention set forth in amended claim 1.

Eisenberg '850 and the Kreisberg paper each also fails to teach each of the following steps in applicants' claimed process for determining experimentally a plurality of three-dimensional atomic structures of proteins: (c) synthesizing for each family determined in step (b), in parallel, a plurality of target proteins, which are appropriately representative members of the family, using information stored in the database corresponding to the plurality of target proteins, and screening products of the synthesis to determine ones that are effective as proteins; (d) preparing, purifying and characterizing each target protein which is determined to be effective in step (c); (e) crystallizing each target protein prepared, purified and characterized in step (d) in parallel against a plurality of crystallization screens to produce a plurality of specimen crystals of the target protein; (f) testing the plurality of specimen crystals of one of the target proteins grown in step (e) for predetermined diffraction characteristics to determine suitable ones of the plurality of specimen crystals of the one target protein; (g) performing high-throughput crystallography, including measuring for diffraction data the specimen crystals of the one target protein determined in step (f) to be suitable, building an atomic model of the one target protein according to an analysis of the diffraction data, refining the model of the one target protein against the diffraction data, and storing the

refined model in the database; and (j) performing steps (f) through (i) for each of the other target proteins, as provided by the invention set forth in amended claim 7.

Therefore, even a combination of the teachings of Eisenberg '850 and the Kreisberg paper in the manner suggested by the Examiner fails to teach or render obvious all features of the claimed invention.

The Examiner apparently is of the opinion that the means/steps for the following which are recited in claims 1 and 7 are well-known in the art and it allegedly would have been obvious to combine the teachings of Eisenberg '850 and the Kreisberg paper with these means/steps as recited in the claims: (1) protein synthesis; (2) protein screening; (3) protein processing; (4) crystallization; and (5) x-ray crystallography.

Applicants respectfully disagree. Applicants submit that the combined teachings of Eisenberg '850 and the Kreisberg paper neither suggest nor provide a motivation for combining the system/method for predicting the protein fold of a target amino acid residue sequence of unknown protein structure according to the teachings of Eisenberg '850 and the Kreisberg paper, with the elements in a system and/or the steps in a process for determining experimentally a plurality of three-dimensional atomic structures, without using applicants' invention as a roadmap.

Although Eisenberg '850 states at column 1, lines 42-46 that the three-dimensional structure of proteins has been determined in a number of ways, including using the technique of X-ray crystallography, Eisenberg '850 also acknowledges at column 2, lines 13-19 that even though there has been a well-recognized need for a means for readily determining a protein's three-dimensional structure from its amino acid sequence, that need has not been adequately met by the then-known techniques of protein structure determination. Thus, it is submitted that one

skilled in the art following the teachings of Eisenberg '850 would not have been motivated to combine, and indeed would have been taught away from combining, a system/method, in accordance with the teachings of Eisenberg '850 and the Kreisberg paper, for predicting the unknown three-dimensional structure of a protein of which its amino acid sequence is known, on the one hand, and elements/steps for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7, on the other hand.

Further, neither Eisenberg '850 nor the Kreisberg paper suggests combining a system/method, in accordance with the teachings of Eisenberg '850 and the Kreisberg paper, for predicting the unknown three-dimensional structure of a protein of which its amino acid sequence is known, with elements/steps for determining experimentally three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7. The teachings of Eisenberg '850 and the Kreisberg paper simply do not suggest or provide motivation for a system/process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7.

Since the teachings of Eisenberg '850 and the Kreisberg paper fail to suggest or provide motivation for a system or a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the invention set forth in amended claims 1 and 7, it would not have been obvious to combine a system/method, in accordance with the teachings of Eisenberg '850 and the Kreisberg paper, for predicting the unknown three-dimensional structure of a protein of which its amino acid sequence is known, on the one hand, with elements/steps, even if the elements/steps individually are known generally to the art,

for determining experimentally a plurality of three-dimensional atomic structures, on the other hand, in the manner suggested by the Examiner, without using the claimed invention as a template.

Applicants maintain that claims 1 and 7 are patentable over Eisenberg '850 in view of the Kreisberg paper.

Regarding claims 2 through 6 applicants respectfully point out that claims 2-6 depend on and include all the limitations of claim 1. Thus, claims 2-6 are patentable at least for the reasons set forth above with respect to claim 1.

Regarding claims 8 through 12 applicants respectfully point out that claims 8-12 depend on and include all the limitations of claim 7. Thus, claims 8-12 are patentable at least for the reasons set forth above with respect to claim 7.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1 through 12 under 35 U.S.C. § 103.

In view of the amendments to the claims and remarks hereinabove, applicants maintain that claims 1 through 12 are now in condition for allowance. Accordingly, applicants earnestly solicit the allowance of claims 1 through 12.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee, other than the enclosed $435.00 fee for the Petition for a Three-Month Extension of Time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents, Washington, D.C. 20231.

4/6/00
John P. White Date
Reg. No. 28,678